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The Effectiveness of Prothrombin Complex Concentrate in Reversing the Anticoagulant Activity of the Oral Direct Thrombin Inhibitor Dabigatran (Pradaxa®): A Review of Human Studies

Abstract

Dabigatran is an oral direct thrombin inhibitor approved by the US FDA for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Dabigatran is rapidly replacing traditional anticoagulants, such as warfarin, despite the fact that clinicians have very little experience with dabigatran induced bleeding and no reliable therapeutic agent to reverse its effects. Prothrombin complex concentrate is effective at reversing traditional anticoagulants as it contains clotting factors, including prothrombin, the precursor to thrombin. How effective is prothrombin complex concentrate in reversing the anticoagulant activity of dabigatran?

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Annjanette Sommers

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**The Effectiveness of Prothrombin Complex Concentrate in Reversing
the Anticoagulant Activity of the Oral Direct Thrombin Inhibitor
Dabigatran (Pradaxa®): A Review of Human Studies**

Bridget Barron



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

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For the Masters of Science Degree, August 10, 2013

Faculty Advisor: Mary Von

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Biography

Bridget Barron is a native of Phoenix, Arizona. She spent 11 years prior to PA school enjoying a career as a Certified Surgical Technologist. Her passion for orthopedics and a young PA named John inspired her to pursue a career beyond surgical technology. After obtaining a Bachelor of Science degree in Psychology she moved to Hillsboro, Oregon to attend Pacific University. She enjoys traveling and photography and plans to pursue a career in orthopedic trauma after graduation.

Abstract

Background: Dabigatran is an oral direct thrombin inhibitor approved by the US FDA for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Dabigatran is rapidly replacing traditional anticoagulants, such as warfarin, despite the fact that clinicians have very little experience with dabigatran induced bleeding and no reliable therapeutic agent to reverse its effects. Prothrombin complex concentrate is effective at reversing traditional anticoagulants as it contains clotting factors, including prothrombin, the precursor to thrombin. How effective is prothrombin complex concentrate in reversing the anticoagulant activity of dabigatran?

Method: An exhaustive literature search using Medline/OVID, CINAHL, and Web of Science was performed using the search terms “dabigatran” and “prothrombin complex concentrate.” The search was limited to human studies. All studies were assessed for quality using the GRADE criteria.

Results: There were 58 results were retrieved from the initial search with only two studies meeting the inclusion criteria. Both studies used coagulation assays as surrogate markers for reversal of dabigatran. A randomized, placebo-controlled, crossover study published in the Netherlands in 2011 studied *in vivo* the effects of the PCC Cofact® on the reversal of dabigatran in healthy male subjects. Cofact was found to have no effect on coagulation assays considered sensitive to dabigatran. A randomized, crossover, ex vivo study published in France in 2012 studied *in vitro* the effects of two PCCs, Kanokad® and FEIBA®, at varying doses on the reversal of dabigatran in healthy male subjects. Kanokad was shown to increase the amount of thrombin generated but only FEIBA corrected kinetic parameters modified by dabigatran.

Conclusion: The data available on the efficacy of PCC in reversing dabigatran is limited and mixed. Differing concentrations of PCC on the market and a lack of clear guidelines regarding dosage amounts further confounds the issue. At least one PCC, Cofact, has been proven ineffective at the studied dose in reversing dabigatran based on coagulation assays. While Kanokad has been shown to increase total thrombin production, only low-dose FEIBA has been proven to affect the kinetic parameters of thrombin generation modified by dabigatran without increased thrombotic risk, suggesting its potential success in clinical use. Further *in vivo* studies in human subjects are needed to validate the efficacy of FEIBA in reversing dabigatran.

Keywords: anticoagulant, Cofact, dabigatran, direct thrombin inhibitor, FEIBA, Kanokad, Pradaxa, prothrombin complex concentrate

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List of Abbreviations

ANOVA.....	Analysis of Variance
aPTT.....	activated Partial Thromboplastin Time
ECT.....	Ecarin Clotting Time
ETP.....	Endogenous Thrombin Potential lag time
ETP-AUC.....	Endogenous Thrombin Potential, Area Under the Curve
FFP.....	Fresh Frozen Plasma
GRADE.....	Grading of Recommendations, Assessment, Development and Evaluations
LT.....	Lag Time
PCC.....	Prothrombin Complex Concentrate
rVIIa.....	activated recombinant Factor VII
TT.....	Thrombin Time
TTP.....	Time To Peak
TGT.....	Thromboplastin Generation Test
VKA.....	Vitamin K Antagonist

The Effectiveness of Prothrombin Complex Concentrate in Reversing the Anticoagulant Activity of the Oral Direct Thrombin Inhibitor Dabigatran (Pradaxa®): A Review of Human Studies

BACKGROUND

Dabigatran (Pradaxa®) is an oral direct thrombin inhibitor that was approved by the US FDA in 2010 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.¹ For over 50 years, the vitamin K antagonist (VKA), warfarin, has been the mainstay of therapy for both short and long-term anticoagulation needs.² Disadvantages of warfarin therapy, such as the need for regular coagulation monitoring and various interactions with food and other drugs,³ prompted research into the development of new drugs with more favorable treatment regimes. In February of 2011, the American College of Cardiology and the American Heart Association made a class I recommendation⁴ for the use of dabigatran as an alternative to warfarin, despite the fact that clinicians have very little experience with dabigatran-induced bleeding and no reliable therapeutic agent to reverse its effects.¹

The results of two large trials provided practitioners with effective alternatives to warfarin therapy. In the RE-LY trial,⁵ dabigatran was found to be more effective than warfarin in the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation. The RE-COVER trial⁶ found dabigatran to be noninferior to warfarin for the treatment of acute venous thromboembolism (VTE), prompting approval of its use for VTE prophylaxis in Europe. While these trials provided new options for providers, they also raised a significant clinical question—how is the potent anticoagulant activity of this new drug reversed?

Although dabigatran-associated bleeding events are considered rare,⁷ significant safety concerns surround its use. In 2011, dabigatran accounted for 3781 adverse events, including 542 deaths (out of 30 385 total deaths reported to the FDA), 2367 reports of hemorrhage, 291 cases of acute renal failure, and 644 cases of stroke. Additionally, it was suspected in 15 cases of liver failure. In comparison, warfarin accounted for 1106 adverse events, including 72 deaths.²

Prothrombin Complex Concentrate

Traditional anticoagulants, such as warfarin, can be effectively reversed with the administration of Fresh Frozen Plasma (FFP) in conjunction with vitamin K, or isolated therapy with 4-factor prothrombin complex concentrate (PCC). The American College of Chest Physicians recently changed their guidelines for the management of reversing VKAs in favor of 4-factor PCC over FFP and vitamin K. However, these are Grade 2C recommendations, meaning there is uncertainty in the risk or benefits and benefits must be carefully balanced with risks.⁸

Prothrombin complex concentrate is effective in reversing warfarin coagulopathy as it replenishes the vitamin K-dependent clotting factors (II, VII, IX, and X), but these effects occur upstream from the site of activity of dabigatran in the clotting cascade.¹ Prothrombin complex concentrate is available in either 3-factor concentrate (contains clotting factors II, IX, and X) or 4-factor concentrate (contains clotting factors II, VII, IX, and X). 4-factor PCC is also available in either activated (FEIBA®) or nonactivated (Cofact®) formulations, but the nonactivated form is not currently available in the US. Both forms of PCC contain small amounts of endogenous anticoagulant proteins C and S, and both are associated with an increased risk of thrombotic events.⁸

Speculation as to the potential efficacy of PCC in the reversal of dabigatran is based on the fact that it contains clotting factors that ultimately lead to the production of factor II, or prothrombin, the precursor to thrombin. Some forms of PCC, such as 4-factor PCC, may also contain an activated form of factor VII (FVIIa), a vital clotting factor in initiating the clotting cascade.⁹ To illustrate why the theory of PCC efficacy in dabigatran reversal is plausible, a brief review of the clotting cascade and dabigatran's site of action are warranted.

The Clotting Cascade

When endothelial injury, or injury to the lining of a blood vessel, occurs a substance called tissue factor (TF) is released into the bloodstream. Primary hemostasis occurs at the site of the injury by the aggregation of platelets. Secondary hemostasis occurs simultaneously in the bloodstream by the activation of coagulation factors. In the bloodstream, TF comes into contact with activated factor VII, one of many procoagulants, or clotting factors, produced by the healthy liver. The coupling of TF and factor VII in the bloodstream triggers a complex chain reaction known as the clotting cascade, ultimately resulting in the formation of a fibrin clot.^{1, 10}

The clotting cascade itself is divided into 2 pathways, intrinsic and extrinsic, that converge in a final common pathway.¹⁰ A simplified version of the clotting cascade demonstrates the site of activity of dabigatran (Figure I).¹ Dabigatran directly inhibits the production of thrombin, a serine protease that is essential to clot formation. Thrombin has several functions, including: catalyzing the conversion of fibrinogen to fibrin, forming a fibrin clot; activation of additional clotting factors responsible for producing more thrombin; initiating platelet aggregation by activating their surface receptors; and

activation of factor XIII, which helps strengthen fibrin bonds in a formed clot. The direct thrombin inhibitors are unique, in that they can inactivate not only free thrombin in the bloodstream, but thrombin already bound to fibrin in a blood clot.¹¹

The fact that no effective antidote exists has raised numerous concerns in the medical community with regard to the potentially devastating outcomes of closed-space bleeding, such as intracranial, pericardial, or spinal.¹ A recent article in the New York Times¹² outlined the concerns of a Houston-based trauma physician, Dr. Bryan A. Cotton, who shared the story of a 70 year-old man taking dabigatran who fell at home, arrived to the emergency room alert and oriented, but subsequently bled to death on the table despite numerous interventions. Concerns of this sort are echoed elsewhere in the medical community via case reports^{13, 14} of difficulty in reversing dabigatran-induced bleeding, including two incidents of gastrointestinal bleeding in patients taking dabigatran that were not successfully stopped with the administration of PCC. One of the patients in the aforementioned cases¹⁴ died of multi-organ failure despite administration of PCC and FFP, although he did have significant medical comorbidities.

The purpose of this review was to determine the efficacy of PCC in reversing the anticoagulant activity of dabigatran in human subjects.

METHODS

An exhaustive literature search using Medline/OVID, CINAHL, and Web of Science was performed using the search terms “dabigatran” and “prothrombin complex concentrate.” The search was limited to human studies. All studies were assessed for quality using the GRADE criteria.¹⁵

RESULTS

Fifty-eight results were retrieved from the initial search with only two studies meeting the inclusion criteria: one randomized, placebo-controlled, crossover study¹⁶ and one randomized, crossover, ex vivo study.¹⁷

Netherlands study

This randomized, placebo-controlled, crossover study¹⁶ in healthy subjects used the coagulation assays aPTT (activated partial thromboplastin time), ETP (endogenous thrombin potential lag time), TT (thrombin time) and ECT (ecarin clotting time) as surrogate markers for reversal of dabigatran and the direct factor Xa inhibitor, rivoroxaban. Cofact (Sanquin Blood Supply, Amsterdam, the Netherlands), a nonactivated 4-factor PCC derived from human plasma, was the chosen PCC.¹⁶

Twelve healthy males of unknown age without any relevant medical history were included in this study. All subjects had normal blood counts and normal kidney and liver function. Additionally, all subjects tested negative for hepatitis B, C and HIV.¹⁶

Subjects were randomized to receive either dabigatran 150mg twice daily or rivaroxaban 20 mg twice daily for 2½ days, with the last dose being given on the third day with no food consumption. On the third day, subjects were admitted to the hospital for infusion of either 50U/kg PCC or a similar volume of saline as placebo. Blood was then collected for 24 hours after the infusion. After a washout period of 11 days, the subjects received treatment with the other anticoagulant drug following the same protocol.¹⁶

Following administration of dabigatran, aPTT was increased from 33.6 ± 3.3 to 59.4 ± 15.8 seconds. Neither PCC nor placebo (saline) had an effect on aPTT, with times

for PCC at 70.3 ± 15.1 seconds; $P=0.21$ and saline at 57.9 ± 10.3 seconds; $P=0.64$. No significant difference was found in aPTT between PCC and placebo ($P=0.13$). aPTT normalized within 24 hours.¹⁶

Following administration of dabigatran, ETP lag time was prolonged from 2.9 ± 0.4 to 7.5 ± 2.5 minutes (mean \pm SD; $P<0.001$). Neither PCC nor saline had an effect on ETP lag time prolongation, with PCC times of 8.7 ± 2.6 minutes; $P=0.20$ and saline times of 8.5 ± 2.2 minutes; $P=0.22$.¹⁶

Following administration of dabigatran, TT increased to >120 seconds, the upper limit, for all subjects. TT remained immeasurable after infusion of both PCC and placebo for beyond 6 hours ($P=0.36$; repeated measures ANOVA).¹⁶

Administration of dabigatran prolonged the ECT from 33.1 ± 1 seconds at baseline to 69 ± 26 seconds after 3 days of dabigatran intake ($P=0.002$). PCC did not reverse the prolongation of ECT but slightly increased it to 86 ± 20 seconds ($P=0.08$). The same pattern of increased ECT was observed with placebo (mean \pm SD, $P=0.08$; repeated measures ANOVA).¹⁶

The authors concluded that Cofact was not effective in reversing the anticoagulant activity of dabigatran based on irreversible prolongation of the aPTT, ETP lag time, TT, and ECT in all subjects.¹⁶

French study

This randomized, crossover, ex-vivo study¹⁷ in healthy volunteers used TGT (thrombin generation test) parameters (Figure II)¹⁸ as surrogate markers for reversal of dabigatran and the direct factor Xa inhibitor, rivaroxaban. Quantitative parameters were ETP-AUC (endogenous thrombin potential, area under the curve) and maximum

thrombin concentration (peak). Kinetic parameters were lag time (LT) and time to reach maximum thrombin concentration (TTP). Kanokad® (LFB, Courtabouef, France), a 4-factor PCC, and activated prothrombin complex concentrate (FEIBA, Baxter AG, Vienna, Austria), were studied in comparison to recombinant activated factor VIIa (rFVIIa, Novoseven®, NovoNordisk, Copenhagen, Denmark). Data for rFVIIa will not be reported in this review.¹⁷

Ten healthy white male subjects (age 18-45) with a body mass index between 18 and 30kg/m² were included in this study. Subjects with a personal or family history of thrombosis or bleeding disorders were excluded, as were those with renal or liver impairment.¹⁷

Subjects were randomized to receive either dabigatran 150mg or rivaroxaban 20mg in one oral dose. No information as given on randomization procedure. Venous blood samples were obtained just before drug administration and 2 hours after administration. The same process was repeated with the other anticoagulant drug after a 15-day washout period. All assays were performed ex vivo.¹⁷

Since no recommendations existed regarding dosage, each hemostatic agent was tested at 3 different concentrations. Kanokad was given at 0.25, 0.5, and 1U/mL; FEIBA at 0.25, 0.5, 1 and 2U/mL.¹⁷

Thrombin generation test parameters were measured at baseline (H0) and 2 hours (H2) after oral intake of 150mg dabigatran. ETP at H0 was 1191(247) and decreased to 953(182) at H2 ($P=0.0013$). Peak at H0 was 227.1(40.2) and decreased to 220.5(49.2) at H2 ($P=0.5$). LT at H0 was 2.15(0.31) and increased to 3.78(1.21) at H2 ($P=0.0009$). TTP was 4.23(0.62) at H0 and increased to 5.4(1.25) at H2 ($P=0.002$).¹⁷

Thrombin generation test parameters were measured again at H2 after administration of either Kanokad or FEIBA. Low doses of Kanokad or FEIBA decreased ETP-AUC close to baseline (approximately 1.5 and 1.6 nM.min, respectively) but higher doses caused a significant increase in thrombin generation (highest doses of Kanokad and FEIBA at 2.6 nM.min).¹⁷

In conclusion, the authors stated that PCCs, especially FEIBA, were reasonable choices for reversing the effects of dabigatran based on the ability of FEIBA at 0.5U/mL to reverse LT to near baseline despite overcorrection of ETP-AUC. The peak of thrombin generation remained below 400nM at the 0.5U/mL dose, with 500nM being the upper threshold for increased thrombotic risk. In light of this, the authors outlined the necessity for further defining the lowest effective dose of FEIBA.¹⁷

DISCUSSION

The question of whether or not PCC can effectively reverse the anticoagulant activity of dabigatran is of critical clinical importance, especially in the setting of major hemorrhage, closed-space bleeding, or the need for emergent surgical intervention. While animal studies^{7,9} have pointed to the efficacy of PCC in reducing bleeding in rabbits and mice, these results cannot reliably be extrapolated to humans. Both studies included in this review aimed to test the effects of hemostatic agents on the anticoagulant activity of dabigatran in humans, and their authors note the necessity for further clinical studies.

The studies were assessed using the Grading of Recommendations, Assessment, Development and Evaluation, or GRADE,¹⁵ criteria. The included studies were downgraded to a very low level of quality of evidence for limitations, such as small

sample size, all-male patient population, inclusion of only healthy patients, limited data in terms of patient demographics, and use of surrogate markers (blood tests). See Table I. Additionally, the French study¹⁷ used *in vitro* vs. *in vivo* testing methods. No evidence of publication bias or crossover effect was evident in either study.

Concerns regarding the use of typical coagulation assays, and the use of other tests not readily available to practicing clinicians, have been brought to light. Traditional clotting assays, such as the aPTT, provide only qualitative information and do not adequately reflect the degree of anticoagulation, thereby raising the question of whether or not such tests can be used as markers of effective reversal.¹ An earlier animal study¹⁹ also questioned the correlation between aPTT and dabigatran reversal, pointing out that aPTT times remained immeasurable after administration of PCC while bleeding times were reduced, a finding that suggests aPTT may not be a reliable indicator of dabigatran reversal. The ECT, which uses snake venom, is considered the clotting test most sensitive to dabigatran and yet is not readily available to most clinicians.²⁰ A cheaper, less-sensitive version of the ECT, the Hemoclot® thrombin inhibitor assay, is also not readily available to many clinicians.

Further studies in human subjects are necessary to determine the true efficacy of PCC in reversing dabigatran. A larger patient population, as well as one more representative of those actually taking the drug for therapy, would yield more meaningful results. The effects of PCC on coagulation of most interest to clinicians would be in the setting of acute hemorrhage, especially closed-space bleeding. However, constructing such trials in humans would be challenging given the relatively rare occurrence of bleeding events. At this point, a reasonable course of action might be to provide major

trauma centers with a PCC shown to have some benefit, such as FEIBA, and to study its efficacy in the patient suffering from dabigatran-induced hemorrhage in conjunction with providing standard resuscitation. Additionally, some physicians have suggested the creation of a national or international registry to monitor bleeding events and their treatment.²¹

To date, the only recommended options for the general treatment of dabigatran induced bleeding are outlined in recommendations published in 2009 for patients taking novel anticoagulant drugs who present with bleeding. Treatment involves supportive care with fluid resuscitation; red blood cell transfusion; diagnostic or therapeutic interventions aimed at identifying the source of bleeding; and application of local hemostatic measures if the site of bleeding is accessible.²²

Additionally, reversal can be treated with measures used in the setting of a typical drug overdose, such as emergent hemodialysis or hemoperfusion, gastric lavage or administration of activated charcoal if the drug has been taken within a few hours. The aforementioned interventions have significant limitations, however, such as the availability of emergent hemodialysis or hemoperfusion and obtaining vascular access in the anticoagulated patient.⁸

CONCLUSION

Ultimately, the data available on the efficacy of PCC in reversing dabigatran is limited and mixed. Differing concentrations of PCC on the market and a lack of clear guidelines regarding dosage amounts further confounds the issue. At least one PCC, Cofact, has been proven ineffective at the studied dose in reversing the anticoagulant

activity of the oral direct thrombin inhibitor dabigatran in human subjects based on coagulation assays. While Kanokad has been shown to increase total thrombin production, only low-dose FEIBA has been proven to affect the kinetic parameters of thrombin generation modified by dabigatran without increased thrombotic risk, suggesting its potential success in clinical use. Further in vivo studies in human subjects are needed to validate the efficacy of FEIBA in reversing dabigatran.

These facts raise significant clinical and ethical considerations when considering dabigatran for treatment. The fact that no antidote has been proven in humans begs the question of whether or not providers should be prescribing the drug so liberally. While it is assumed that providers fully disclose the associated risks and benefits of a specific drug therapy to patients, too often this is not the case. These studies outline the critical importance of choosing the right drug for the right patient, and carefully weighing increased benefits with associated risks.

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TABLE 1 Characteristics of Reviewed Studies, GRADE profile

Quality Assessment							Summary of Findings					Importance						
Downgrade criteria																		
Design	Methodology	Indirectness	Imprecision	Inconsistency	Publication bias likely	Quality	Study	Treatment (total)	Value before dabigatran	Value after dabigatran 150mg ^a	Value after PCC							
Netherlands (in vivo) study ¹⁶																		
Randomized Placebo Controlled Crossover Study	No serious limitations	No serious limitations	Serious limitations ^d	No serious limitations	No serious limitations	Very low	aPTT	6	33.6 +/- 3.3 seconds	59.4 +/- 15.8 seconds	Cofact ^b	Less important						
												No effect	Critical					
							ETP lag time	6	2.9 +/- 0.4 minutes	7.5 +/- 2.5 minutes	No effect	Important						
							TT	6	20 seconds	> 120 seconds	> 120 seconds	Critical						
French (ex vivo) ¹⁷																		
Randomized Controlled Crossover Ex-vivo Study	No serious limitations	Serious limitations ^d	Serious limitations ^d	No serious limitations	No serious limitations	Very low	ETP-AUC	5	H0 ¹ : 1191 (247) nM.min	H2 ² : 953 (182) nM.min	Kanokad ^c	FEIBA ^c	Important					
											1.50	1.60						
											1.90	1.80						
											2.60	2.40						
																	2.60	
							Peak	5	H0: 227.1 (40.2) nM	H2: 220.5 (49.2) nM	296.2±57.3	361±28	Critical					
											Data not given	Data not given						
											462.1±81.9	Data not given						
							LT	5	H0: 2.16 (0.31) seconds	H2: 3.78 (1.21) seconds	551.7±99.5		Important					
											0.90	0.80						
											0.89	0.71						
											0.89	0.70						
							TTP ³	5	H0: 4.23 (0.62) seconds	H2: 5.4 (1.25) seconds			Important					

- ^a Netherlands study used dabigatran 150 mg, 2 times daily dosing with measurements taken after 2½ days
French study used measurements taken at baseline and 2 hours after administration of dabigatran 150mg
- ^b Netherlands study used Cofact 50U/kg
- ^c French study used Kanokad at 3 concentration: 0.25U/mL, 0.5U/mL and 1U/mL and FEIBA at 4 concentrations: 0.25U/mL, 0.5U/mL, 1U/mL, and 2U, mL
- ^d Netherlands study was downgraded for small sample size; French study was downgraded for small sample size and use of *in vitro* testing methods

- ¹ H0 = baseline measurement at hour zero
- ² H2 = measurement 2 hours after administration of dabigatran 150mg
- ³ TTP data was not given as TTP was found to correlate strongly with LT

Values in **ORANGE** are estimated from bar graphs on p 1577 of Netherlands study and p 222 of French study. Data are expressed as mean relative change from H2 ± SD.

Figure I: Clotting cascade and site of activity of dabigatran¹

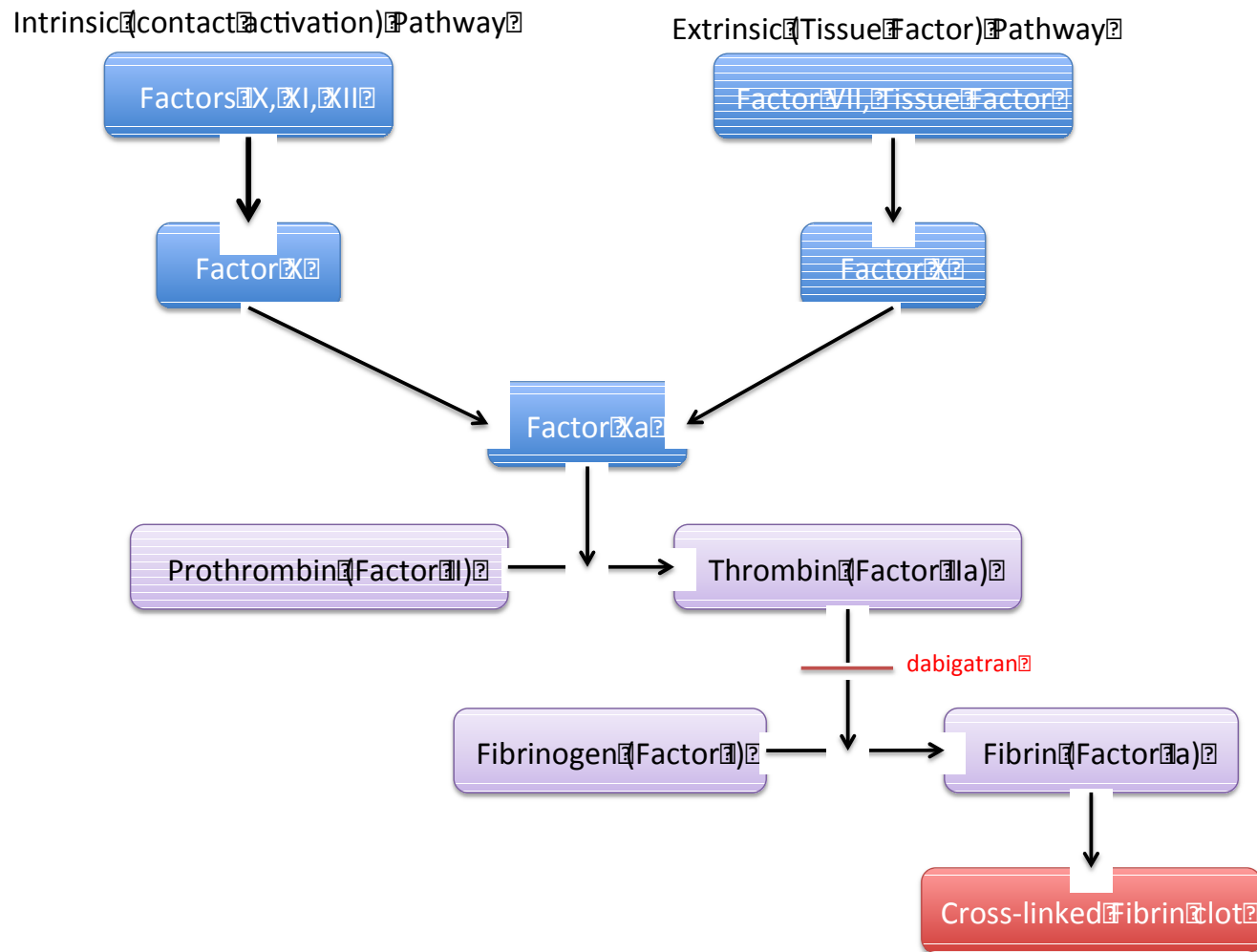


Figure II: Thrombin Generation Test (TGT) parameters¹⁸

